A Risk Assessment of Uranium in Drinking Water

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Summary

Naturally occurring uranium is known to give rise to adverse renal effects in various species after ingestion. This short review of uranium toxicity focus on three epidemiological studies on drinking water which are compared with a pivotal study in experimental animals used as a basis for limits of uranium in drinking water or guidelines in several countries. These studies are scrutinized and discussed, and it is suggested that authorities in this particular case to a higher extent should make use of epidemiological data in their evaluation. Finally, based on epidemiological data an intervention level for uranium in Swedish drinking water is proposed, namely 15 microgram per litre.

Background

Soluble uranium salts occur naturally in drinking water in certain areas of Sweden and to an even greater degree in Finland and certain other countries, for instance Ireland. In such areas, uranium intake from other dietary sources than water is of marginal importance. The soluble uranium salts in water are absorbed to a few percent in the intestine. A large proportion of the uranium absorbed is rapidly excreted in the urine but some accumulation occurs in the renal cortex and in the skeleton.

Experimental studies on animals indicate that uranium in high doses produces functional and morphological effects on the proximal tubule in the kidney. These functional effects include reduced reabsorption, resulting in increased excretion of e.g. calcium, phosphate, glucose and low molecular weight proteins such as β-2-microglobulin (BMG). Uranium induced cell mortality in tubules of experimental animals leads to leakage of enzymes (e.g. alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase and N-acetyl-β-D-glucosaminidase=NAG; e.g. Anthony et al; 1994).
Epidemiological studies

Drinking water

Four studies are reported in the literature up to 2002. The first, which can be regarded as more of a pilot study (initially 133 individuals), was carried out in 1983-1985 in Nova Scotia, Canada. A total of 324 individuals (1/3 controls) including 191 additional recruits were exposed to up to 700 μg uranium/L in drinking water. Urine and hair were analysed for uranium. The results showed a trend towards increased BMG excretion, which it was possible to correlate to the uranium concentration in the drinking water (Moss et al., 1983). It was also possible to relate the uranium concentration in hair to exposure to uranium in drinking water.

Study 2 was carried out in 1993 in Saskatchewan, Canada (Mao et al., 1995). Three areas with average uranium concentrations of 0.71 μg (0.48-0.74; control), 19.6 μg (0.1-48) and 14.7 μg (0.1-50) per litre water were chosen for the study. The control group comprised 40 individuals, the other groups 30 individuals each. Age varied between 18-84 years for the individuals, of whom one-third were male and two-thirds female. Blood and urine samples were taken from the participants. The uranium concentration in the water and albumin and creatinine concentrations in urine were analysed (and compared against serum creatinine concentrations in blood). It was possible to correlate an increase in albumin concentration in the urine to exposure to uranium in the drinking water (see Appendix 2 for details).

Study 3 compared people with private wells from a village in Nova Scotia, Canada, to a control group in Ottawa who used municipal drinking water (Zamora et al., 1998). The concentrations of uranium in well water occasionally exceeded 100 μg (max. 780 μg) per litre water. The water used by the control group had a concentration of <1 μg per litre water. In total, this study only comprised 50 individuals (17 men and 33 women) in the age range 14-87 years, of which the control group was made up of 20 individuals who had drunk their water for 1-33 years and the exposed group of 30 individuals who had drunk their water for 3-59 years, although with pooled water samples for both groups. Data on uranium intake were obtained via duplicate portions of food and water. Urine was collected over one day. Glucose, total protein, creatinine, alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase and NAG concentrations were determined. BMG was analysed separately via night urine. There was a trend (not statistically significant) for increased concentrations of glucose, alkaline phosphatase and BMG in the urine that were correlated to exposure, indicating changes in the tubule (see Appendix 2 for details).

The most recent study, from 1999, concerned residents in southern Finland (Kurttio et al., 2002) and comprised 325 individuals aged 15-82 with private wells who had drunk their well water for 1-34 years (average 13 years). These individuals were divided into 3 groups, with exposure to <10 μg/L, 10-100 μg/L or > 100 μg/L. Maximum exposure was 1920 μg uranium/L in the drinking water.
(median concentration 28 μg/L). Daily uranium intake was 39 μg (median 7-224 μg). Water, urine and blood were analysed. Indicators of renal function (proximal tubule) were BMG, glucose, calcium and phosphate ions, while those of glomerulus function were creatinine excretion and albumin in the urine. A positive correlation was reported between uranium concentration in the urine and increased calcium and phosphate excretion in the urine, and between calcium excretion and uranium in the drinking water. This indicates effects on renal tubular function that were shown to be significant at uranium concentrations in drinking water of above 300 μg/L. The correlation between renal toxicity effects and uranium in the urine was greater than the correlation between renal toxicity effects and uranium in the water. No correlation was found between effects and cumulative intake. The conclusion was that short-term exposure appears to be most relevant for renal toxicity effects (see Appendix 2 for details).

Other studies

Studies of relationships between urinary uranium and kidney effects in workers exposed to uranium and in soldiers exposed through “friendly fire” to depleted uranium give perspective on the drinking water studies.

In a study of 39 U.S. workers exposed by inhalation for an average of 10 years in uranium mills, there were slight effects on the proximal tubule (increased excretion of BMG and amino acids; Thun et al 1985; Table 1). The median excretion of uranium in urine was about 6 μg/L.

In a small study of 13 Egyptian uranium mill workers, there were some indications of an effect on the kidney (increased serum creatinine) in the four workers with the highest urinary uranium excretion (about 29 μg/L; Shawky et al 2002; Table 1).

Soldiers exposed to “friendly fire” may retain uranium fragments in the body. In 39 U.S. veterans, subjects with retained uranium fragments had higher urinary uranium concentrations than those without (McDarmid et al 2004; Table 1). Further, the persons with retained fragments (median urinary uranium about 2 μg/g creatinine) displayed indications of slight effects on the proximal tubule (increased excretion of total protein and retinal binding protein, though not of BMG).
Animal studies

The Gilman study

The critical toxicity study that forms the basis of (various) national limits for uranium in drinking water:

Gilman et al. (1998a) carried out a 91-day study on Sprague-Dawley rats (15 of each sex) that were given uranyl nitrate hexahydrate in the drinking water in concentrations of 0.96, 4.8, 24, 120 and 600 mg/L (corresponding to 0.06, 0.3, 1.5, 7.5 and 36.7 mg uranium/kg body weight/day). The control group received tapwater. Haematological and biochemical parameters were determined after the exposure period and a histopathological investigation was performed. No treatment-related haematological effects were observed. Histopathological changes were observed mainly in the liver, thyroid gland and kidney. In the liver, treatment-related effects were observed in both sexes at all doses and these were commonly non-specific changes in the nucleus and cytoplasm. The effects on the thyroid gland were non-specific for the uranium treatment. The kidney was the organ most affected. In male rats, statistically significant treatment-related effects on the kidney were obtained at all doses, although not dose related, and included nuclear vesiculation, cytoplasmic vacuolation and tubular dilation. Other statistically significant lesions in male rats (at the 4.8 mg/L dose and above) included glomerular adhesions, apical displacement of the proximal tubular epithelial nuclei and cytoplasmic degranulation. In female rats, statistically significant changes were induced in kidneys, including nuclear vesiculation of the tubular epithelial nuclei and anisokaryosis at all doses except that of 4.8 mg/L. However, the most important changes in female rats were capsular sclerosis (hardening) of the glomeruli and reticulin sclerosis of the interstitial membranes. These changes were observed at all doses and were regarded as non-repairable lesions. Significant treatment-related liver changes were also reported in hepatic nuclei and cytoplasm in both sexes at the lowest exposure level. The LOAEL (lowest adverse effect level) for adverse effects on the kidney and liver of male and female rats was based on the frequency of degenerative lesions in the renal proximal convoluted tubule at the level 0.96 mg uranyl nitrate hexahydrate per litre water (corresponding to 0.09 mg uranium/kg bw/day in female rats and 0.06 mg/kg bw/day in male rats). The reason for the difference in sensitivity between male and female rats was not clear, but does not appear to be due to differences in pharmacokinetics, since accumulation of uranium in renal tissue did not differ significantly between the sexes at any of the given doses.
Comments on the Gilman study

The study was comprehensive and included e.g. a range of histopathological observations in kidney and liver. The study was well-executed but perhaps greater attention should have been paid to the fact that the 28-day preliminary study with the doses 0.96, 4.8, 24, 120 and 600 mg uranyl nitrate/L (same range of doses as in the 91-day study) did not show any significant effects on food or liquid intake or growth, or any haematological or clinical differences between the control group and the exposed groups. Histopathological effects occurred in the 91-day study from even the lowest dose, 0.96 mg uranyl nitrate hexahydrate per litre drinking water, up to the highest dose of 600 mg uranyl nitrate hexahydrate per litre drinking water. However, no dose-response relationship was found for the effects reported, which is remarkable. Additional data reported more serious effects at higher doses without providing the basis on which this evaluation was made. Even more remarkable is the fact that no treatment-related haematological effects were observed at any dose, not even the highest dose of 600 mg uranyl nitrate hexahydrate per litre drinking water. Clinical-chemical studies, which would have provided valuable information on kidney status, were lacking. The conclusions were based entirely on the histopathological effects, which should have been complemented with biochemical parameters determined in the urine to give more weight to the overall conclusion, particularly as only a LOAEL could be established. Also, the exposure time may be short, considering the long-term accumulation (in the skeleton, which causes endogenous exposure of the kidney). Finally, the time at which the study was carried out can be questioned, since according to the authors of the article, certain data were reported as early as 1982 and 1985, i.e. up to 16 years before the publication discussed here.
Discussion and conclusions

The most comprehensive sub-chronic oral study on uranium (Gilman et al., 1998a), in which rats were given uranium via the drinking water, forms the basis for several national limits for uranium in drinking water, even though these are not in agreement with each other. The size of the safety factor, allocation of total intake to water or food, daily intake of drinking water, body weight, etc. give rise to the differences between national limits or guideline values. In the absence of long-term studies (2 years) on experimental animals, this study has been used, although only a LOAEL could be established and not a NOAEL (no adverse effect level). The WHO’s motivation for not adding an extra safety factor to the 100 used to determine the previous limit¹ (9 µg/L drinking water) for uranium in drinking water is as follows:

“The effects observed in the animal study cannot be regarded as severe and, based on the estimated 15-day biological half-life of uranium in the kidneys of experimental animals, it is not justifiable to use an extra safety factor on the basis of the results of this short 90-day study, since the effects on kidneys should not increase with time.”

However, it appears that a dose-response relationship is lacking for the effects in this study (comment by the Swedish National Food Administration, see above). Several objections to this study are included above in the section ‘Comments on the Gilman study’.

Three epidemiological studies on people who had drunk water containing uranium were evaluated, of which the most recent (Kurtio et al., 2002) and most comprehensive was considered to be the most relevant. It shows a very weak effect of uranium in the water on renal function, more specifically in the renal tubule. One of the other two studies, from Canada, can support this, even though it has a considerably lower value as evidence. On the other hand, it can be seen as complementing the Finnish study, since it seems to show similar effects on the kidney. This finding also agrees with experiences in experimental animals.

Mild effects on renal tubule are probably reversible if the exposure decreases. However, with chronic exposure other possibilities must be considered: Loss of calcium through the urine has a negative effect on calcium balance and this could increase the risk of osteoporosis. At the present time, knowledge is lacking in this area. The Finnish study – possibly with some support from the Canadian study – shows that effects on the kidneys occur at uranium concentrations in water of a few hundred micrograms/litre or more. Effects may occur at lower concentrations,

¹ Based on an LOAEL of 60 µg/kg bw/day in the animal study by Gilman et al. (1998a), a safety factor of 100 (10 X for extrapolation between species, 10 X for individual variation) is used, which gives 0.6 µg /kg bw/day and this multiplied by a body weight of 60 kg gives 36 µg /day for an individual. Half is allocated to drinking water, i.e. 18 µg at maximum should be taken in via standard consumption of 2 L/day, so the guideline value is 9 µg/L drinking water.
but this cannot be determined with the existing data, nor can it be determined with certainty whether chronic exposure increases the risk. Continued research is therefore imperative.

There is much to show that greater emphasis should have been placed on these epidemiological studies, particularly in the most recent one (comment by the Swedish National Food Administration). In the most recent, there was also a clear correlation between renal toxicity effects and uranium in the urine, which therefore reveals actual exposure to uranium in the kidney.

An alternative way to use the complete set of epidemiological data, from both the drinking water studies and the other ones is shown in Table 1. The levels in kidney has been estimated from uranium intake and urinary uranium levels by use of metabolic models. Then, it seems that slight effects on the kidney occur at kidney uranium levels of about 0.01 μg/g, or higher. The corresponding excretion in urine is about 0.7 μg/g creatinine (about 0.7 μg/L).

Table 1. Relationship between exposure to uranium levels in urine (medians in groups where effects have been reported), calculated concentrations in the kidney and toxic effects on the kidney in man.

<table>
<thead>
<tr>
<th>Source</th>
<th>Years</th>
<th>N</th>
<th>Uranium in water (μg/L)</th>
<th>Uranium intake (μg/d)</th>
<th>Uranium in kidney (μg/g)</th>
<th>Uranium in urine</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking water</td>
<td>~ 20</td>
<td>50</td>
<td>~ 100</td>
<td>~ 20</td>
<td>(0,01)</td>
<td>-</td>
<td>+</td>
<td>Limson et al 1998</td>
</tr>
<tr>
<td>Drinking water</td>
<td>13</td>
<td>325</td>
<td>~ 135</td>
<td>~ 224</td>
<td>(0,009-0,04)</td>
<td>~ 0,7μg/g creatinine</td>
<td>++</td>
<td>Kurttio et al 2002</td>
</tr>
<tr>
<td>Drinking water</td>
<td>10</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>(0,03)</td>
<td>~ 2 μg/g creatinine</td>
<td>+</td>
<td>Mc Darmid et al 2004</td>
</tr>
<tr>
<td>Occupational</td>
<td>13</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>(0,4)</td>
<td>~ 29 μg/L</td>
<td>(+)</td>
<td>Shawky et al 2002</td>
</tr>
<tr>
<td>Occupational</td>
<td>10</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>(0,08)</td>
<td>~ 6 μg/L</td>
<td>++</td>
<td>Thun et al 1985</td>
</tr>
</tbody>
</table>

Intake of all uranium from water (if the intake is not given) 2 L/d. The mass of uranium in the kidney corresponds to 6.6 % of the daily intake after 10 years. Kidney weight 350 g. It is assumed, that the gastro-intestinal absorption is 2 %. The excretion of urine is assumed to be 1.6 L/d (ICRP 2003; 1.5 g creatinine/d) and that the absorbed amount corresponds to the excretion in urine. Metabolism according to the model by the International Commission on Radiological Protection (ICRP 1995; Leggett 1994; Chen et al 2004).++ Reasonably well established effect; + probable effect; (+) possible effect.
Proposed intervention levels for uranium in drinking water

The epidemiological studies of uranium in drinking water indicate that effects on the kidney can arise after long-term intake of uranium in high concentrations, at least from a few hundred micrograms per litre drinking water and above. However, no safe lower limit could be defined. The reported effects were slight, but must be considered adverse; they may decrease the margin to sustain effects of other insults on the kidney, e.g. by other kidney disorders. On the other hand, it is possible that they are reversible, if the exposure decreases. Also, several studies of mortality from kidney disease in uranium workers have not shown increased risks, though a “healthy worker effect” may have obscured the picture (Royal Society 2002).

When deriving a TDI, the dose at which no effects are observed in humans is generally divided by a factor of 10 to take into account individual variation with respect to health effects of exposure to chemical substances. A relatively large safety margin is warranted by the fact that the data base is meagre and fasting intake and iron deficiency increases the absorption.

Using a safety margin of 10, one arrives at a concentration of around 20-30 micrograms of uranium per litre drinking water for normal daily consumption (2 litres) if a safety factor of 10 is used on the basis of the effects in the Finnish epidemiological study (from approx. 200-300 μg/L drinking water and above). This concentration is in agreement with the limits set for uranium in Canada (20 μg/L drinking water) and the USA (30 μg/L drinking water) based on the animal study by Gilman et al. (1998a; see for some reasons for the differences in these limits). The WHO has now an official limit of 15 μg/L drinking water (80 % allocation to drinking water).

An adult subject who drinks 2 L of water containing 15 μg/L will obtain a uranium level in the kidney of about 0.005 μg/g and a urinary excretion of about 0.4 μg/g creatinine (by the model used in Table 1). This may be compared to the estimated critical uranium levels in man of 0.01 μg/g kidney and about 0.7 μg/g creatinine in urine. Hence, the safety margin may not be large. However, the calculations has several uncertainties. For example, the absorption rate of uranium from water may be over-estimated (Karpas et al 2005), which would increase the safety margin.

For comparison, morphologic effects in the rabbit kidney were noted at 0.02 μg/g (Gilman et al 1998). Further, in a study of Swedish young men, the median level of uranium in urine was 0.059 μg/g creatinine (Sandström and Nygren 2001; Sandström 2002). The three subjects with the highest levels had 0.105-0.143 μg/g creatinine. They lived in a community with a drinking water uranium level of 18 μg/L.
In a one-year old infant (9 kg body weight) with high intake of water (67 mL/kg body weight/day vs about 30 mL/kg/day in adults; USEPA 2002), gastrointestinal absorption (3 % vs 2 % in adults), kidney weight 1 % of body weight, calculations by a model (Chen et al 2004) indicates a kidney uranium concentration of 0.006 μg/g at a drinking-water level of 15 μg/L. This estimate is uncertain, in particular since the absorption in infants is unclear; neonatal pigs have a much higher absorption than adult pigs. Also, it is not known whether or not the infant kidney is more sensitive than the adult one, as regards toxic effects of heavy metals (Solhaug et al 2004).

The above reasoning based on the animal study by Gilman et al. (despite its limitations) and on the epidemiological data indicates that upper level (limit) for uranium in drinking water in Sweden should not exceed 15 μg/L drinking water.

From mapping uranium concentrations in municipal drinking water in Sweden just recently, levels up to 41 μg uranium/L drinking water have been recorded. However, it is unusual that levels exceed 30 μg uranium/L. From analysis of drinking water from private wells in Sweden, in the area of lake Mälaren, levels of almost 150 μg uranium/L have been recorded and in the county of Värmland up to almost 400 μg uranium/L. In Finland even higher levels have been found in private wells; up to 15 mg uranium/L drinking water.
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Appendix 1

Short review of toxicological data

Radiation risk
The radiation dose from natural uranium is small (30 μg uranium/L drinking water corresponds to a radiation dose of 0.02-0.04 mSv per year) compared with the natural background exposure (2-4 mSv) to which residents in Sweden are subjected daily, and is thus insignificant in the present context.

Absorption, distribution, metabolism and excretion
Many uranium compounds are insoluble and are not absorbed in the body. The more soluble forms are absorbed to a few percent (Wrenn et al., 1985): For intake together with food, there are indications that between 10 and 30 % (Berlin & Rudell, 1986) can be taken up, but in the presence of oxidising compounds even more can be taken up (Sullivan et al., 1986). In the blood, the uranium mainly occurs complex-bound to bicarbonate, protein and red blood cells (Fisenne & Perry, 1985). Release from the blood is rapid and thus the uranium is eventually accumulated, primarily in the skeleton (85 %, replaces calcium; La Touche et al., 1987) and 90 % of the remainder mainly in the kidneys.

The average half-life in humans under normal conditions is estimated at 180-360 days (Berlin & Rudell, 1986). However, in the skeleton the half-life is considerably longer; 300 and 5000 days for clearance from the skeleton in the rat have been estimated (Wrenn et al., 1985). Total body content of soluble uranium in humans is approx. 40 μg (Igarashi et al., 1987).

Acute (chemical) toxicity
The LD₅₀ in mouse and rats respectively has been reported to be 204 and 242 mg/kg bw of uranyl ethanoate dihydrate (Domingo et al., 1987). The effects observed included weight loss, piloerection and haemorrhages in the eyes, legs and nose. The most common effect of uranium on the kidneys of experimental animals is disruption of renal function: proximal convoluted tubules. A newly discovered mechanism shows that the uranyl ion inhibits use of ATP-ases via its effects on Na⁺-dependent and -independent transport systems and on mitochon-
drial oxidative phosphorylation in the proximal tubule (Domingo, 1995). Another suggested mechanism proposes that bicarbonate-bound uranium in the blood is filtered through the glomerulus and excreted in the urine. The rate of excretion is dependent on the pH of the urine. At low pH, dissociation of uranium and bicarbonate occurs. The uranyl ion formed can then be bound to proteins on the surface of cells in the tubule and cause cell membrane damage. Morphological changes and tissue changes in kidney cells have been reported and these can be reversible. Tissue changes seem to reverse relatively rapidly, but not the biochemical processes (Leggett, 1989). There is possibly a certain tolerance to repeated uranium exposure (Campbell, 1985).

**Sub-acute effects**

The chemical toxicity of uranium is mainly directed at the kidneys, but the cardiovascular system, liver and central nervous system can also be affected.

Dosing 40 Sprague-Dawley rats with 0-16 mg uranyl ethanoate dihydrate/kg bw/day (corresponding to 0-9 mg uranium/kg bw/day) in the drinking water for 2 weeks (Ortega et al., 1989) resulted in biochemical changes such as increased blood glucose concentration (at the dose 4 mg/kg bw/day), decreases in alanine transferase and aspartame transferase (8 mg/kg bw/day), blood changes (16 mg/kg bw/day) and increased protein levels in the urine at all doses. The NOAEL was determined to be 2 mg uranyl ethanoate dihydrate/kg bw/day (1.1 mg uranium/kg bw/day).

**Sub-chronic effects**

See in particular Gilman et al. (1998a), reported earlier in section 3.

Dosing 10 New Zealand rabbits with 0, 0.96, 4.8, 24, 120 and 600 mg uranyl nitrate hexahydrate/L drinking water (corresponding to 0, 0.05, 0.2, 0.88, 4.82 and 29 mg uranium/kg bw/day) for 91 days (Gilman et al., 1998b) resulted in tissue changes in kidney, liver, thyroid gland and aorta. A LOAEL of 0.05 mg uranium/kg bw/day was determined, based on changes in the kidney. At the highest dose, a total of 11 different types of injury were observed in the kidney. When the study was repeated (4 of the rabbits in the first study were not Pasteurella free and became infected) with fewer doses (0, 0.49, 1.32 and 43 mg uranium/kg bw/day, similar effects were obtained even at the lowest dose of 0.49 mg/kg bw/day (LOAEL). The effects were less distinct in females even though they received higher doses of uranium (via greater drinking water consumption). A pharmacokinetic sex difference may exist.

Dosing 5-8 New Zealand rabbits with 0, 24 and 600 mg uranyl nitrate hexahydrate/kg bw in the drinking water (corresponding to 0, 1.36 and 41 mg uranium/kg
bw/day) for 91 days (Gilman et al., 1998c) plus 91 days of recovery led to smaller tissue changes in liver, thyroid gland and aorta. Residual effects on the kidney were observed in the highest dose group after the recovery period. The LOAEL was estimated to be somewhere between 1.36-41 mg uranium/kg bw/day for effects on the kidney.

**Chronic toxicity**

High doses (up to 20 % in the diet) of various uranium compounds administered to rats, rabbits and dogs for periods from 30 days to 2 years produced effects on the kidney in all species (Maynard & Hodge, 1949).

**Reproductive and developmental toxicity**

Administration of 2 % uranyl nitrate hexahydrate to rats for 7 months decreased total number of foetuses and average litter size (Maynard & Hodge, 1949).

Twenty Swiss mice (females) per group fed 0, 5, 10, 25 and 50 mg uranyl acetate dihydrate/kg bw/day (corresponding to 0, 2.8, 5.6, 14 and 28 mg uranium/kg bw/day) by gavage during days 6-15 of gestation and killed after 18 days (Domingo et al., 1989a) displayed reduced weight gain (from the 2.8 mg dose ->), lower feed intake (from the 5.6 mg dose ->) and increased liver weight (from the 2.8 mg dose ->). In the offspring, reduced weight and length gain, undeveloped foetuses, an increased number of external and internal abnormalities and an increased number of developmental abnormalities were observed at the lowest dose. At the next highest dose (14 mg uranium kg/bw/day), effects such as cleft palate, bipartite sternebrae and developmental variations such as reduced or absent ossification were observed. No embryo lethality was observed. Based on both the maternal and foetotoxic effects, a LOAEL of 2.8 mg uranium/kg bw/day was considered.

Twenty Swiss mice (females) per group fed 0, 0.05, 0.5, 5 and 50 mg uranyl acetate dihydrate/kg bw/day (corresponding to 0, 0.028, 0.28, 2.8 and 28 mg uranium/kg bw/day) by gavage from day 13 of gestation to day 21 during lactation (Domingo et al., 1989b) displayed maternal mortality of 2/20 (2.8 mg uranium/kg bw) and 3/20 (28 mg uranium/kg bw) as well as reduced liver weight at all doses. In the offspring, decreased survival was observed at the highest dose, as well as reduced suckling in the remaining animals. Based on the developmental effects in the offspring, a NOEL of 2.8 mg uranium/kg bw/day was established.

Twenty-five Swiss mice (males) per group were dosed with 0, 5, 10 and 25 mg uranyl acetate dihydrate/kg bw/day (corresponding to 0, 2.8, 5,6 and 14 mg uranium/kg bw/day) orally for 60 days before mating (Paternain et al., 1989).
Females were exposed from 14 days before mating until the end of the lactation period. No effects on fertility were observed. In the offspring, increased embryo lethality (late implantations and dead foetuses) was observed at the highest dose. From the 5.6 mg uranium/kg bw/day dose, increased foetus mortality and reduced growth and development of offspring from birth and throughout suckling were observed.

Non-specific degenerative changes in the testicles of rats after chronic exposure to uranyl nitrate hexadecahydrate and uranyl fluoride have been reported (Maynard & Hodge, 1949; Maynard et al., 1953; Malenchenko et al., 1978).

Swiss mice (males) dosed with 0, 10, 20, 40 and 80 mg uranyl acetate dihydrate/kg bw/day (corresponding to 0, 5.6, 11.2, 22.4 and 44.8 mg uranium/kg bw/day) in the drinking water for 64 days (Llobet et al., 1991) were mated with unexposed females for 4 days. No functional effects on testicles were observed but there was a non-dose related decline in gestation rate.

**Carcinogenicity**

No carcinogenic effects of administering doses of soluble or insoluble uranium to experimental animals have been demonstrated (Wrenn et al., 1985).

**Mutagenicity**

Uranyl nitrate has been shown to be cytotoxic and genotoxic in CHO cells (0.01-0.3 mmol/L; Lin et al., 1993). Dose-related effects such as reduced survival, disrupted cell cycles, increased frequency of micronuclei (*in vitro*), SCE and chromosome aberrations were observed. The genotoxic effect was attributed to uranyl nitrate binding to phosphate groups in DNA. Chromosome aberrations have also been observed in germ cells from male mice after treatment with enriched uranyl fluoride. However, the possibility that the effect was due to the radioactivity of the substance could not be ruled out (Hu & Zhu, 1990).

**Effects on humans**

Kidney inflammation is the essential acute effect of exposure to uranium (Hursch & Spoor, 1973).

For chronic effects via drinking water, see section 1 and Appendix 2.
Appendix 2

Epidemiological evaluation

by Professor Staffan Skerfving

Evaluation of the epidemiological studies was carried out by Professor Staffan Skerfving on behalf of the Toxicology Division, Swedish National Food Administration.


This investigation was carried out in Saskatchewan, Canada, in 1993. Three regions were selected, unclear exactly on what grounds. One area (control) was known to have low levels of uranium in the drinking water, two considerably higher. Randomly selected telephone numbers were called and adults who replied were asked to participate in the study. Calling continued until a pre-determined number of people had been recruited. In the control area, 40 people were recruited, which corresponded to 22% of telephone numbers called, while there were 30 recruits in each of two areas with high uranium concentrations, corresponding to 39% and 50% of numbers called respectively. The total group consisted of 36% men and 64% woman, with ages varying between 18 and 84 years. In the control area, 28% ≥60 years, in the two uranium areas 27% and 50% respectively.

A nurse visited the home. A questionnaire was used to obtain information on how long the person had lived in the house and how many cups of water he/she drank at home per day (data not shown). Individuals were reported to be ‘asymptomatic’. Information on ‘diabetes status’ was obtained in an unspecified way, and the number defined as having diabetes is not specified. It is also apparent that the study considered gender, occupational exposure, water filtration and heredity of serious kidney disease.

One to three unfiltered water samples were taken from drinking water taps (from private wells or municipal water supply, relative distribution unclear) over the course of several days and 30 field-filtered (once or twice) water samples (0.45 μm). It is not clear whether the water was allowed to run before sampling.
Samples were analysed using inductively coupled plasma mass spectrometry (ICP-MS; detection limit not specified, but probably < 0.1 μg/L; precision < 8 %; accuracy < 5 % according to external quality control samples). It is stated generally that the concentration varied little between samples and that filtration had no effect. The mean uranium concentration in water in the control group was 0.71 μg/L (range of variation 0.48-0.74 μg/L), while in the two high uranium groups it was 20 (< 0.1-48) and 15 (< 0.1-50) μg/L. Silicon concentration in the water was also determined and a strong correlation was found with the uranium concentration (r=0.66).

Blood samples were taken for determination of serum creatinine, while albumin and creatinine were determined in morning urine samples. The data supplied on methodology are incomplete but the method for albumin determination is sensitive, precision not specified. To compensate for variations in degree of dilution of the urine, the uranium concentration was expressed in relation to creatinine. It is not clear whether all analyses were carried out at one laboratory and in one operation. Data relating to albumin concentration are given in a very general way and only for the entire material combined. It is obvious that there is a skewed distribution.

Statistical analysis of the material was carried out with parametric methods and without transformation, and no report is made of whether the justification for this had been tested. No comparison was made between the groups and the data were not reported separately for the three groups, but simply pooled.

The results are reported very tersely. There was no significant relationship between the albumin concentration in urine or serum creatinine and the uranium concentration in water. When an exposure index was constructed on the basis of uranium concentration in the individual’s drinking water, number of cups drunk per day and number of years the water had been drunk (data for individuals or groups not reported), there was a relatively strong age-related correlation with both uranium concentration/creatinine (r=0.39) and silicon/creatinine (r=0.32), both of which were probably statistically significant. There was a weaker correlation between exposure index and serum creatinine (r=0.18). No graphs of the relationships are provided.

In a linear multiple regression that included age, ‘diabetes status’ and silicon concentration in water, there was no significant increase in uranium/creatinine, but a non-statistically significant (P=0.03) increase with increasing exposure index (the slope cannot be interpreted since the units are unclear).

**Comments**
The authors refer to the study as ‘preliminary’, since the exposure parameter was approximate and the number of participants small. In addition, the highest uranium concentration in water was low.
The study has a number of methodological weaknesses: Drop-out rate is high and varies between the groups, so the scope for selection is large, even though it is not possible to determine whether this can have caused a false positive relationship between uranium exposure and albuminuria. A proportion of the individuals drank water from private wells, the rest municipal water; there is reason to suspect that this also involved other differences (socio-economic, etc.) that may have been confounding. The reporting of results is unacceptably terse. The authors admittedly adjusted the albumin in urine for degree of dilution but did not take into consideration the variation caused by the albumin concentration in serum. Albumin-creatinine clearance would surely have been a more appropriate measure of the status of the glomerular membrane.

It is difficult to understand the authors’ thinking behind the analysis model. They included silicon, which has a strong correlation with uranium but which does not itself bear any relation to the effect parameter (and no well-established link to kidney damage). This would have led to an overcorrection and a weakening of the relationship between uranium and albumin, thus a bias towards zero.

There was no relationship with measured concentrations of uranium and albumin, only with the cumulative exposure index. This creates interpretation difficulties, since no details are available of uranium concentrations in the past. It is known that the concentration can vary. However, this would more probably have limited the potential for identifying a relationship.

A greater problem is that this index would probably show a covariance with age, which is a risk factor for albuminuria. There is a very great variation in age, and also a difference between the groups. Therefore, there is a risk of confounding problems. It is not clear whether this was successfully adjusted for in the multivariate statistical model. The authors do not discuss other potential confounders. They state that they have adjusted for diabetes (which is a significant cause of albuminuria), but provide no data. However, diabetes would more likely be an effect modifier rather than a confounder. Another important effect modifier not taken into account is hypertonia, although this would probably have masked any relationship with uranium. In addition, medication (e.g. analgesics) would have been able to modify the effect. The nephrotoxic elements lead, cadmium and mercury were apparently also determined in the water, but there were no differences between groups and thus no cause to suspect confounding.

The authors actually report one single statistically significant relationship as the outcome of a great number of tests; there is an obvious mass significance issue. The effect that they thought they observed happens to be discrete from a clinical perspective, since only eight individuals had ‘elevated’ albumin concentrations (unclear how this was defined). This is supported by the fact that there was no relationship between uranium serum creatinine or between serum creatinine and albumin. However, serum creatinine only begins to increase after a substantial
decline in glomerular filtration rate (GFR). In addition, the concentrations of uranium in the water were not particularly high.

Summary
This study was small and had considerable deficiencies in methodology and data reporting. The concentration gradient of uranium in water was skewed. This is in principle compatible with a discrete effect of long-term exposure to uranium concentrations in drinking water of 50 μg/L, involving either slight leakage across the glomerular membrane and/or a decrease in reabsorption of albumin in the proximal renal tubules, but this is far from conclusive.

The study subjects recruited in Canada, from a village in Nova Scotia with private (drilled) wells in an area with high uranium concentrations (occasionally >100 µg/L), and a city (Ottawa) with municipal water (surface) with low concentrations (<1 µg/L). Recruitment is unclear, residents in the village were ‘approached’ (the aim was to have a uniform gender and age distribution within 20-70 years, these objectives clearly not being achieved, see below). In Ottawa, a (presumably stratified) matching was carried out for gender and age compared to the village. Nine people were excluded on health grounds.

In total, the study comprised only 50 individuals (17 men and 33 women). Age varied between 14 and 87 years. Subjects had drunk the water in question for 0-51 years.

Samples of tapwater were taken, unclear how. They were analysed for uranium with ICP-MS. The detection limit was 0.0006 µg/L. Precision was checked by addition of radioactive uranium. The precision is not reported.

Uranium concentrations in water from the village and from Ottawa are not specified. Instead, all individuals who had <1 µg/L were pooled in a ‘low-exposure group’ (N=20; uranium concentration in the municipal water in this group was 0.02±0.004 µg/L) and all with ≥1 µg/L in a ‘high-exposure group’ (N=30; uranium concentration in water 2-780 µg/L, of which half over 100 µg/L). This would mean that Ottawa and the village dominated their respective group, but also that there was Ottawa water with concentrations >1 µg/L. This presumably also means that the groups were dominated by people with completely different socio-economic backgrounds. Gender and age distribution was uniform between the groups.

The researchers also collected duplicate portions of food and water for 3 days. Urine was analysed. Specific data on the analyses are not given. In the high exposure group, uranium intake from food and water was 3-570 µg/day (of which 31-98 % from water), in the low exposure group 0.32-20 µg/day (of which 1-9 % from water).

Urine was collected for 24 hours. Determination of glucose, total protein, creatinine, ALP, GGT, LDH and NAG was carried out using standard methods. Detection limits are given. The precision in replicate determinations was ≤11 %. There was a considerable (up to 62 %) intra-individual variation in different urine portions during the 24 hours studied. It is stated that uranium was also measured but this information is not reported.
Night-time urine was also collected for determination of BMG (40 samples analysed). This urine was alkalised with phosphate buffer in the laboratory. However, it is doubtful whether this was sufficient to prevent breakdown in acidic urine.

The researchers tested whether the biomarkers and their logarithms were normally distributed. This was not the case, so they used non-parametric tests.

In total, 18 analyses of biomarkers exceeded the upper reference limit in the literature, which was possibly more than one might expect.

The concentration of glucose (mg/day) was significantly (Kruskal-Wallis test) higher (47 %) in the high uranium group than in the low. An effect can also be seen on LDH, but only in men and in the wrong direction. For protein (mg/day), ALP, GGT and NAG (all uranium/g creatinine), there were no significant differences.

There were significant (P<0.05) rank correlations between uranium intake (from water and food) and glucose (rS=0.40, significant in both men and women), BMG (rS=0.39; only in men) and ALP, but not protein, GGT or NAG.

**Comments**

This study was small and suffered from clear methodological and data handling problems.

The most significant fault is that individuals selected for the high and low uranium groups were recruited in areas that presumably had completely different socio-economic structures. It is unclear how test subjects were found. This leaves room for bias in the form of confounding from e.g. occupational exposure and lifestyle factors (diet, smoking, etc.).

The researchers also carried out an unacceptably primitive statistical analysis of the data they had and did not consider potential confounding and effect modification. An obvious risk for confounding lies in age, which could have been associated with both uranium intake and effect markers (which are age-dependent), all of which have a known age-dependency. It is possible to calculate the correlation between age and uranium intake from the data in the article; there is a relationship but it is not statistically significant. The fact that effect modification by e.g. gender, age and medication was not taken into account is rather to the disadvantage of the hypothesis, since these introduce an unadjusted variation in the outcome, which would confuse the picture.

It is difficult to understand why the researchers did not use the uranium concentrations in urine to which they clearly had access.
A multivariate regression model, with systematic adjustment for potential confounders and effect modifiers, would have given greater credibility to the results; however, the researchers would have had to test other types of transformations of the effect markers than logarithmic. They would then have been able to obtain more confidence-inspiring estimates of the effects, e.g. as regression coefficients with uncertainty levels. On the other hand, the material was too small for advanced analysis.

There is no information on previous uranium exposure. It was known how long the individuals drank the water in question (down to 0 years!) but no attempt was made to investigate whether this had an influence on the effect.

The strength of the study lies in the fact that both water and food were analysed (which verified that water was the dominant source in the area with high concentrations) and that a long list of biomarkers were used for effects on renal tubule. An effect was found on BMG, which is a classic marker for proximal tubular function disruption. It is surprising that no increased excretion of NAG was observed, since this is usually an early symptom of cell damage in the tubule.

**Summary**

The study has considerable failings in methodology and data reporting. The findings of exposure-related effects on excretion of glucose, BMG and ALP are in principle compatible with a discrete effect on renal tubule at uranium concentrations in water of less than 780 μg/L. However, they are not conclusive. No conclusions are drawn on the level at which effects appear.
This study was carried out in 1999. Questionnaires were sent to 798 households in 28 towns in southern Finland where high uranium concentrations had been measured and many measurements carried out, according to a drinking water database of drilled wells. A second questionnaire on e.g. residence time, drinking water use, work history, exposure to heavy metals, health status and use of medication was sent to 436 adults who drank water from drilled wells. Of these, 78 % agreed to participate in the study. Fourteen were excluded on the grounds of e.g. water filtration, diabetes (N=4) or use of medication. The study thus comprised 325 people in total (uniform gender distribution, average age 52 years, range of variation 15-82 years) with 194 wells in 24 towns. They had drunk well water for 13 (1-34) years. Some stratification after uranium concentrations in water was obviously carried out.

The individuals collected drinking water in the evening. The water was analysed for uranium using ICP-MS (detection limit 0.0004 μg/L; precision in duplicate samples 3 %; accuracy good in external quality control). The median concentration was 28 μg/L (range 0.0001-1.920 μg/L; the lowest value is not consistent with how values below the detection limit were said to be treated). Daily uranium intake with water was 39 μg (7-224 μg), cumulative intake from the well 129 mg (24-887 mg). All these distributions are skewed, but this does not affect the results of the statistical analysis.

Urine was collected during the night (time and volume recorded). Uranium was analysed using ICP-MS. The detection limit was 0.002 μg/L. The precision in the duplicate samples was 16 % (single analysis result used). Data concerning accuracy are not specified, apparently they trusted the external quality control for water-uranium.

In the night samples, creatinine, glucose, phosphate and albumin were analysed. Random samples of urine were collected the next morning for determination of BMG; the samples were alkalised to avoid breakdown. Blood samples were taken for determination of creatinine, calcium, phosphate, glucose and BMG. The methods were sensitive except for BMG, where a massive 65 % lay below the detection limit. The analyses were carried out at a clinical chemical laboratory, which usually implies good quality control. Blood pressure was measured.

Data were analysed using a general linear model, with adjustment for the effect modifiers gender, age and body mass index, the last-named for unknown reasons; analysis of blood pressure also for smoking, again for unknown reasons. Tests were carried out to check whether the effect markers were normally distributed, which the authors claim they were, although this appears doubtful for BMG. A
test was also carried out in which the effect variables were logarithmised, but this did not affect the results, which indicates robustness.

There was a very elegant relationship between uranium concentration in water and in urine.

There was a significant relationship between fractional excretion of calcium (*i.e.* urine-calcium corrected for serum-calcium and creatinine in serum and urine) and urine-uranium (μg/mmol creatinine), water-uranium and daily uranium intake. A graph is presented of urine-uranium, with imposed ‘smoothed running means’, which does not show any apparent threshold, but when different concentration strata are systematically analysed, there is a statistically significant effect (compared with the lowest group) in the highest group (300-1920 μg/L). The same applied to daily intake, while for water-uranium no stratum was significantly elevated. The effect over the entire concentration area of urine-uranium is approx. 30 %.

There was a significant relationship between fractional excretion of phosphate and urine-uranium, but not water-uranium or daily uranium intake. When the different concentration strata are analysed for urine-uranium, there is a statistically significant effect compared with the lowest in the group, the same applied for water-uranium and daily intake. The effect over the entire concentration area of urine-uranium is approx. 50 %.

There were significant relationships between diastolic blood pressure and water-uranium, and daily intake, but not urine-uranium. Diastolic blood pressure increased with urine-uranium, water-uranium and daily intake. The increases over the entire urine-uranium range were approx. 7 and 8 mm Hg. Nocturnal diuresis also increased (approx. 50 %) with urine-uranium (but not the other two exposure parameters).

The time during which the water was used or cumulative uranium intake was not associated with the afore-mentioned parameters.

No relationship was found between excretion rate of glucose (μmol/min) or albumin (μg/min), concentration of BMG (ng/L) in urine or creatinine clearance on the one hand, and urine-uranium, water-uranium or daily intake on the other.

**Comments**

This was a well-executed study, with clear design and acceptable drop-out rate. A strength lies in the fact that the authors used urine-uranium as an exposure parameter; it showed the strongest relationship with the effects. The authors emphasize that uranium concentration in urine does not have the problem with variation over time suffered by uranium concentration in water or the errors of memory associated with data on water intake.
However, the analytical error is not negligible and experiences from other heavy metals indicate variations in time, although this would have reduced the possibility of verifying any relationships, e.g. for glucose, albumin and BMG. There are other factors that could have decreased the potential to observe effects. For unknown reasons, the authors treated the three factors above in a different way to calcium and phosphate, i.e. they did not calculate creatinine-corrected clearance, which would have given ‘harder’ values not affected by diuresis and serum concentrations. In the case of BMG, this may have been due to the fact that the analysis unfortunately did not have sufficient sensitivity for the purpose. The study was designed to ensure a 20 % increase in BMG and creatinine-clearance (although unclear which exposure markers and strata). Such effects did not exist.

It is unfortunate that the authors did not utilise other low-molecular proteins (e.g. α-1-microglobulin, which is a sensitive measure of the effects of other heavy metals).

The authors appear to have dealt with confounding (incl. heavy metals) and effect modifiers (gender, age, medication, diabetes, etc.) in an appropriate way, through exclusions and adjustments or through adequate discussion.

Summary
The effect of calcium and phosphate excretion may indicate defective reabsorption in the proximal tubule. This effect is relatively discrete. Too small an effect would also indicate that there was no relationship with BMG and glucose excretion, but here the authors presumably had too blunt an instrument. No information is given on uranium intake via food, but the Canadian data discussed above indicate that water is the totally dominant source when the concentration is high. Furthermore, this absence would if anything lead to difficulties in demonstrating true relationships.

The authors could not discern any threshold. This is admittedly true, but the material available would not permit sound conclusions on the issue and the only attempt made simply shows that confirmed effects were only present in the group with concentrations in water of 300-1920 μg/L. The possibility surely existed to more closely analyse the dose-response.

The effect on diuresis, unless a random effect depending on the number of statistical analyses, would indicate an effect on the distal tubule, with decreased resorption of water. The effects on blood pressure are more difficult to explain mechanistically.

The authors found no relationship between their markers for glomerular function. However, conclusions must be drawn carefully here, since albumin level (leakage over the membrane) and creatinine clearance (glomerular filtration) are not
optimal. Therefore a certain effect on the glomeruli cannot be absolutely excluded.

**Conclusions based on all three studies and health relevance of the results**

The three studies evaluated are of highly variable quality. The Finnish is the best by far. It is also published in a reputable journal. It indicates that there is a discrete (sub-clinical) effect of uranium in water on the function (reabsorption of calcium and phosphate) of the proximal tubule. The better of the Canadian studies can support this, even though its value as evidence is considerably weaker. On the other hand, it can be regarded as complementary, since there seem to be effects on reabsorption of low molecular weight proteins and enzyme leakage. The finding also agrees with experiences from animal experiments and is biologically plausible in view of retention of uranium in the renal tubule.

If one accepts that there is a risk of effects on the proximal tubule from exposure to uranium in water, one must of course evaluate the potential health consequences of this. Slight effects on the proximal tubule are probably reversible if exposure decreases.

However, with chronic exposure one must consider other possibilities: A loss through urine has a negative effect on calcium balance, which could increase the risk of osteoporosis. From studies on cadmium, we know that the risk of reduced bone density and fractures increases with increasing exposure, negative calcium balance being a conceivable mechanism. The etiological fraction is admittedly probably small, but osteoporosis is a common condition.

It is also known that effects on the proximal tubule can lead to effects on other parts of the nephron, with decreased GFR. Cadmium can cause renal failure, at least at high exposure.

In the Finnish study, there was a relationship between uranium exposure and increased blood pressure. The mechanism is not clear, mediation via an effect on the kidneys is a possibility. If a causal relationship were to exist, it would probably be more important from a health perspective than the kidney effect *per se*.

Even if these effects are discrete, they must be regarded as unacceptable (adverse) from an environmental medicine perspective and should form the basis for the establishment of acceptable tolerable intake and limit values in water.

The Finnish study – possibly with support from the better of the Canadian studies – indicates that effects appear at uranium concentrations in water of a few hundred μg/L or above. Effects may exist at lower concentrations, but this could not be decided with the existing data, nor could it be determined with confidence whether chronic exposure increased the risk.
In general terms, more than one good epidemiological study would be required to confirm whether exposure poses a risk, since epidemiological studies are always marred by methodological and interpretation problems (while at the same time having other great advantages over animal experiments). Continued research is therefore imperative.
4. Examination of Residues in Live Animals Products – Results of the Control 2003 by I Nordlander.
15. Synen på tillsyn – utvärdering av tillsyn vid anläggningar med Livsmedelsverkets som tillsynsmyndighet av M Ljung.
22. Risk profile. Virus in food and drinking water in Sweden – Norovirus and Hepatitis A virus by F Lund and R Lindqvist.
4. Utvärdering av första etappen av projektet God livsmedelskvalitet i Västernorrland av H Nordenfors och U Fäger.